

MATHEMATICAL MODELLING OF VARIABLE POROSITY COATINGS FOR DUAL DRUG DELIVERY

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SUMMARY

In this paper we describe a theoretical mathematical model of dual drug delivery from a durable polymer coated medical device. We demonstrate how the release rate of each drug may in principle be controlled by altering the initial loading configuration of the two drugs. By varying the underlying microstructure of polymer coating, further control may be obtained, providing the opportunity to tailor the release profile of each drug for the given application.

Key words: *Drug delivery, variable porosity, coupled partial differential equations*

1 INTRODUCTION

The topic of controlled drug delivery has received much attention in recent years, for example in the design of tablets [1] and local drug delivery devices such as stents [2], transdermal patches [3], contact lenses [4] and orthopaedic implants [5]. A key predictor of performance is the drug release profile. Drug delivery is usually initially tested in an in-vitro environment to assess the range of release profiles that can be obtained and to test the repeatability of the drug coating process, before conducting animal or human trials. The disadvantage of a purely experimental approach is that the experiments need to be repeated whenever system parameters are changed. A mathematical model, on the other hand, can potentially provide useful insight into the effect of varying system parameters. In this paper we focus on dual drug delivery, i.e. the delivery of two drugs from a tablet/device. Depending on the particular application in question, it may be desirable for the drugs to be released at similar rates, or perhaps one of the drugs released rapidly with the other being eluted over a longer period of time. In the case of drug-eluting stents, for example, devices which release an anti-proliferative and a ‘pro-healing’ drug have been proposed, whilst a combination of two of the early drug-eluting stent drugs - Paclitaxel and sirolimus - has also been suggested. Motivated by today’s advances in micro and nanotechnology, we propose variable porosity multi-layer coatings as an additional means of controlling the dual drug delivery and tailoring the release profile to the desired application.

2 METHODOLOGY

2.1 Dual drug delivery

In Figure 1 we display the situation that we wish to model: either a single durable polymer coating layer containing two drugs mixed together, or two coating layers with the two drugs loaded separately in each layer. Since the coating thickness (L) is typically considerably smaller than the lateral dimensions, we restrict our attention to a one-dimensional model, with x representing the single spatial variable. In this preliminary analysis, we assume that the polymer/drug coating has been designed such that diffusion is the principal release mechanism. We further assume that both drug species are dilute, i.e. the presence of one drug does not influence the transport of the other. Under this assumption, the transport of both drugs may be treated separately and we therefore have two diffusion equations for the concentrations, c_1 and c_2 , of drugs 1 and 2, respectively:

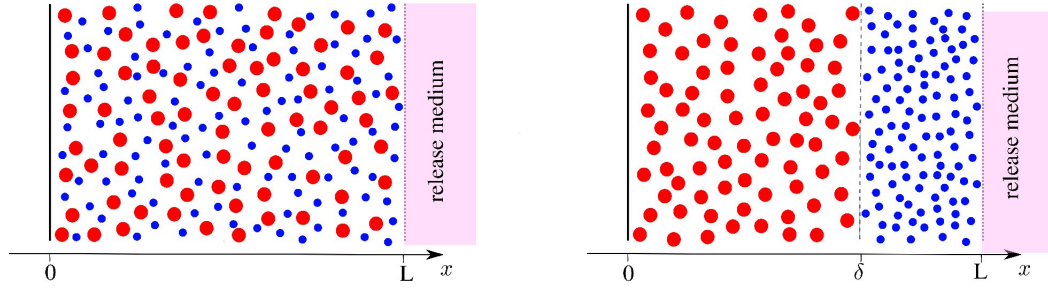


Figure 1: Sketch of two possible initial configurations of a dual drug delivery system. At initial time, the drugs may be uniformly mixed (left, Case 1) in a single layer of thickness L or loaded separately over two layers (right, Case 2), with δ the thickness of the first layer. $x = 0$ and $x = L$ correspond to the interface with the device backing and release medium, respectively. Figure not to scale.

$$\frac{\partial c_1}{\partial t} = D_1 \frac{\partial^2 c_1}{\partial x^2}, \quad \frac{\partial c_2}{\partial t} = D_2 \frac{\partial^2 c_2}{\partial x^2}, \quad 0 < x < L, \quad t > 0. \quad (1)$$

Here, D_1 and D_2 are the effective diffusion coefficients of the respective drugs: these may incorporate many other physical and microstructural parameters, such as porosity and tortuosity (see Section 2.2)

Since our focus is to model in-vitro drug release, we impose an impermeable condition at $x = 0$ and zero concentration at $x = L$, where it is assumed that sink conditions are maintained:

$$-D_1 \frac{\partial c_1}{\partial x} = -D_2 \frac{\partial c_2}{\partial x} = 0, \quad x = 0, \quad t > 0, \quad (2)$$

$$c_1 = c_2 = 0, \quad x = L, \quad t > 0. \quad (3)$$

We model three sets of initial conditions, describing Case 1 and Case 2 above (Figure 1) as well as a more general case (Case 3).

Case 1: drugs are uniformly distributed in the coating at initial constant concentrations c_1^0 and c_2^0 :

$$c_1(x, 0) = c_1^0, \quad c_2(x, 0) = c_2^0, \quad 0 \leq x \leq L. \quad (4)$$

Case 2: drugs are initially contained within two separate layers at constant concentrations:

$$c_1(x, 0) = \begin{cases} c_1^0, & 0 \leq x \leq \delta \\ 0, & \delta < x \leq L, \end{cases} \quad c_2(x, 0) = \begin{cases} 0, & 0 \leq x \leq \delta \\ c_2^0, & \delta < x \leq L. \end{cases} \quad (5)$$

Case 3: Drugs are assigned general spatially varying initial concentration profiles $f(x)$ and $g(x)$:

$$c_1(x, 0) = f(x), \quad c_2(x, 0) = g(x), \quad 0 \leq x \leq L. \quad (6)$$

In the assumption of dilute concentrations, c_1 and c_2 may be solved for independently. By separation of variables, concentrations and masses may be expressed analytically as Fourier expansions.

2.2 Varying the underlying microstructure

The effective diffusion coefficients D_1 and D_2 are not only drug-dependent, but they will also vary depending on the underlying microstructure of the coating. These are related to the porosity ϕ and tortuosity τ of the coating, and to the free diffusion coefficient of the drug (D_1^f and D_2^f) via:

$$D_1 = \frac{\phi D_1^f}{\tau}, \quad D_2 = \frac{\phi D_2^f}{\tau}.$$

Therefore, it is clear that by simulating release profiles for various values of D_1 and D_2 we can not only capture the effect of different drugs, but also different coating microstructural properties, providing further flexibility for tailoring the release profiles for a given application. In addition, the drugs may be released from multi-layer coatings, with varying microstructure between layers (e.g. Figure 2).

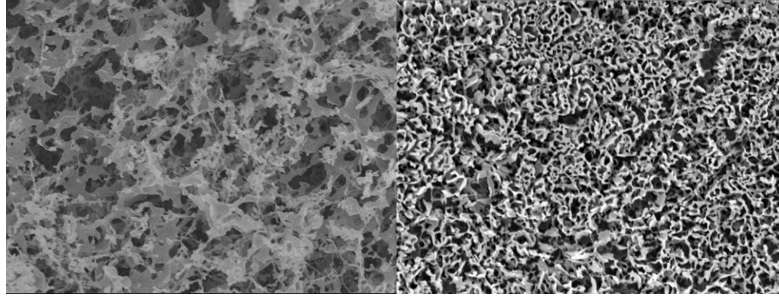


Figure 2: Two adjacent polymer coatings with different microstructural properties

3 RESULTS AND CONCLUSIONS

For the purposes of this study, we are interested in assessing the effect of the loading configuration on the release profiles of each drug, when the initial total mass of drug per unit area (M_1^0 and M_2^0) are assigned fixed quantities:

$$\int_0^L c_1(x, 0)dx = M_1^0, \quad \int_0^L c_2(x, 0)dx = M_2^0. \quad (7)$$

In Figure 3 we consider two uniformly mixed drugs (Case 1) and demonstrate that markedly different release profiles may be obtained simply by varying the effective diffusion coefficients and initial loading masses of the drugs. In Figure 4 we consider two drugs loaded separately in two adjacent

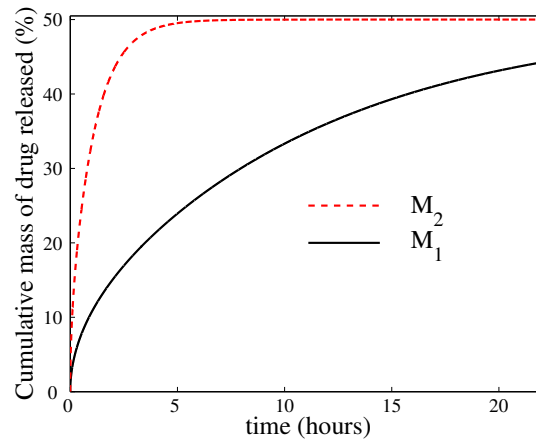


Figure 3: Release profiles of drug 1 and 2 uniformly mixed (Case 1).

layers (Case 2) and demonstrate that we can also in this case obtain very different release profiles. In particular, simply by varying the relative thickness of the layers, the release of the drug in the first layer may be delayed, which could be desirable in certain applications. With this relatively simple mathematical model, it is straightforward to assess the effect of varying the drug (via the diffusion coefficient) and initial loading mass and configuration on the resulting release profile. Moreover, by varying the effective diffusion coefficients, the effect of changes in underlying porosity and tortuosity on the release profiles may be investigated.

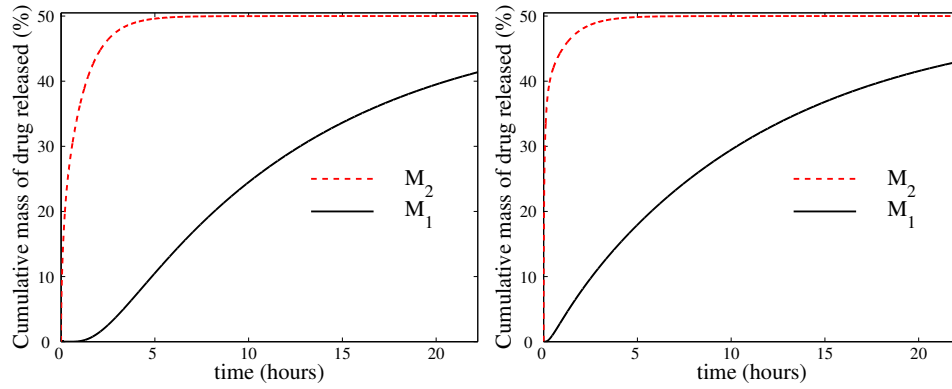


Figure 4: Release profiles of drug 1 and 2 (Case 2). Left: $\delta = L/4$. Right: $\delta = 3L/4$.

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